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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	)	Group Art Unit: 1642
	)	
TALOR	)	Examiner: Gary B. Nickol
	)	
Serial No. 10/611,914	)	
	)	
Filed: July 03, 2003	)	

For: **A METHOD OF PRE-SENSITIZING CANCER PRIOR TO TREATMENT WITH RADIATION AND/OR CHEMOTHERAPY AND A NOVEL CYTOKINE MIXTURE**

DISCUSSION OF NEWLY CITED REFERENCE

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

Applicant previously submitted a petition to make special the above-identified application under 37 C.F.R. § 1.102. The petition was granted on February 10, 2004.

However, Applicant recently became aware of new references and now cites those new references in an enclosed Information Disclosure Statement.

In order to expedite prosecution as well as being in line with the requirement under 37 C.F.R. § 1.102, a detailed discussion of how the invention is patentable over each of the new references is provided in this Discussion of Newly Cited References.

REMARKS

Claims 1-41 are presently pending in the captioned application.

Subsequent to the preliminary amendment submitted herewith, claims 26, 30, 32-33, 35-37 and 39-41 are currently amended and claims 1-25, 27-29, 31, 34 and 38 are as originally filed. The pending claims relate to a standardized mitogen-free and serum-free cytokine mixture having specific ratios of the cytokines IL-1β, TNF-α, IFN-γ and GM-CSF to the cytokine IL-2 (Interleukin 2).

In particular, the presently claimed standardized mitogen-free and serum-free cytokine mixture is effective in inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M. Entry into the proliferative cycle increases vulnerability of the cancerous cell to chemotherapy and radiation therapy.

Evidence from Phase I/II clinical trials clearly demonstrate that the presently claimed invention dramatically improves disease free survival. See "The Effect of Leukocyte Interleukin Injection (Multikine®) Treatment on Peritumoral and Intratumoral Subpopulation of Mononuclear Cells and on Tumor Epithelia: A Possible New Approach to Augmenting Sensitivity to Radiation Therapy and Chemotherapy in Oral Cancer - A Multicenter Phase I/II Clinical Trial", Timar et al., Laryngoscope 113, page 2206-2217,

(December 2003).

However, Applicant has recently become aware of new references subsequent to the previously submitted petition to make special filed on July 30, 2003, and now files an Information Disclosure Statement citing those references. Applicant also encloses a detailed discussion of how the invention is patentable over each of the references as is required under 37 C.F.R. § 1.102.

Applicant submits herewith a Declaration filed under § 1.132 by the inventor Dr. Eyal Talor showing that the present invention only has trace amounts of IL-12 with a mean value of 42 pg/ml. A mean value of 42 pg/ml is outside the specifically disclosed range of 100-10,000 pg/ml of IL-12 disclosed by the submitted references as discussed infra.

In view of the following, Applicant respectfully submits that the presently claimed invention is patentable over each of the newly cited references.

Cited References

Applicant has recently become aware of the following patents and published applications. The following patents and published applications relate to production processes for cytokine mixtures having various cytokines that are applied to diseases and

particularly those diseases related to cancer.

1. U.S. 4,401,756 ("Gillis")

2. U.S. 5,632,983 ("Hadden '983")

3. U.S. 5,698,194 ("Hadden '194")

4. U.S. 2002/0150552 ("Lau et al. 2002/'552")

5. U.S. 2002/0150541 ("Lau et al. 2002/'541")

6. U.S. 2003/0129162 ("Lau et al. 2003/'162")

7. U.S. 2002/0146397 ("Hadden 2002/'397")

8. U.S. 2003/0206885 ("Hadden 2003/'885")

9. U.S. 2003/0124136 ("Hadden 2003/'136")

In view of the following discussion of the references, Applicant respectfully requests accelerated examination of the above-identified application and allowance of the presently pending claims.

Discussion of the References

1. U.S. 4,401,756 ("Gillis") Process for Preparing Human Interleukin 2.

Gillis teaches a production process for preparing Interleukin 2 products from human malignant cells which involves culturing the cells *in vitro* in a serum containing medium supplemented with

additives. Culture is stimulated by an optimum concentration of T-cell mitogen to produce a supernate containing IL-2. The supernate is collected and processed to purify the IL-2. Gillis also teaches the use of phytohemagglutinin as a stimulant mitogen.

The presently claimed invention is patentable over Gillis because the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught by Gillis.

Gillis also fails to teach the novel ranges of cytokines in a cytokine mixture effective in inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy and radiation therapy.

Clearly, the presently claimed invention is not anticipated nor rendered obvious by the Gillis patent.

2. U.S. 5,632,983 ("Hadden '983") Method for Treating Secondary Immunodeficiency

Hadden '983 relates to a treatment of cellular immune deficiency including the steps of determining the presence of a cellular immune deficiency and co-administering an effective amount of thymic peptide combined with an effective amount of

immunomodulating natural non-recombinant cytokine preparation where the immunomodulating natural non-recombinant cytokine preparation is a natural cytokine mixture produced according to U.S. 5,698,194 ("Hadden '194") as discussed infra and having the cytokine profile for the supernatant provided in Col. 7, lines 24-34.

The presently claimed invention is patentable over Hadden '983 because the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught by Hadden '983. Although Hadden '983 teaches broad ranges of the four cytokines IL-2, IL-1, TNF-α, IFN-γ and GM-CSF, the cytokine profile of Hadden '983 specifically **includes** IL-**12** in an amount of 100-10,000 pg/ml. See Hadden '983 at Col. 7, lines 8-19.

In contrast, the present invention only has trace amounts of IL-12 with a mean value of 42 pg/ml. See Table 7 of the Talor Declaration. A mean value of 42 pg/ml is clearly outside the specifically disclosed range of 100-10,000 pg/ml of IL-12 disclosed by Hadden '893. Since the composition of Hadden '893 is specifically limited to a cytokine mixture that **must** contain IL-12 in amounts of 100-100,000 pg/ml, the presently claimed invention which only has a mean value of IL-12 of 42 pg/ml, is unanticipated by the reference.

The ranges disclosed in the cytokine profile of Hadden '893

are calculated by dividing the smallest amount of cytokine disclosed by the largest amount of IL-2. Therefore, the lower limit for the ratio disclosed by Hadden '893 for IL-1 is 10 pg/ml divided by 500 units/ml, which is 0.02. The maximum is 20, which is calculated by dividing the largest amount of IL-1 (2000 pg/ml) by the smallest value of IL-2 (100 units/ml). The putative range of IL-1 to IL-2 is therefore 0.02 to 20 (NOTE: It is unclear as to the type of IL-1 being disclosed by Hadden '893 since only IL-1 is disclosed even though IL-1 comprises various forms such as IL-1β). The IL-2 is measured by ELISA (R&D systems), which is the same as that used by Applicant.

By making the same calculations for IL-12 it can be seen that IL-12 is disclosed by Hadden '893 to be in a ratio range of 0.2-100 and in amounts of 100-10,000 pg/ml. But as shown in the Talor Declaration submitted herewith, IL-12 of the claimed invention has a mean value of IL-12 of 42 pg/ml.

Applicant further notes that IL-3 of Hadden '893 is present in trace amounts. Trace amounts for IL-3 are any measured value of cytokines less than 31 pg/ml, which is the threshold detection level for ELISA produced by R&D systems.

Regarding an obviousness rejection under § 103, Applicant notes that nothing in Hadden '893 relates to the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2

to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF where those ratios induce cancerous cells to enter a proliferative cell cycle phase thereby increasing their vulnerability to follow-on chemotherapy and radiation therapy. The revolutionary discovery of inducing cancer cells into a proliferative cell cycle with the presently claimed ratios is precisely the sort of unexpected result that imparts patentability over the broadly disclosed ranges of Hadden '893.

Based on the clear and unobvious differences from the teachings of Hadden '893, Applicant respectfully submits that the presently claimed invention is not anticipated nor rendered obvious by Hadden '893.

3. U.S. 5,698,194 ("Hadden '194") Method for Making a Medicament For Treating Secondary Immunodeficiency

Hadden '194 is directed to a method for making the medicament comprising the natural cytokine mixture, wherein an isolated population of lymphocytes free of neutrophils and erythrocytes is suspended in a serum free media in a culture vessel with an immobilized mitogen. The mitogen is preferably phytohemagglutinin and the culturing takes place in the continuous presence of a 4-aminoquinolone antibiotic. The process is described in Col. 6-8

and the profile of the resulting cytokine mixture is shown in Col. 7, lines 24-34. Notably, the disclosed cytokine profile of Hadden '194 is the same as that of Hadden '893 as discussed supra.

Applicant respectfully submits that the presently claimed invention is patentable over Hadden '194 for the same reasons as it is patentable over Hadden '893. In particular, Hadden '194 does not teach the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF. Although Hadden '194 teaches broad ranges of the four cytokines IL-2, IL-1, TNF-α, IFN-γ and GM-CSF, the cytokine profile of Hadden '194 specifically **includes** IL-**12** in an amount of 100-10,000 pg/ml. See id.

In contrast, the presently claimed composition only has trace amounts of IL-12 with a mean value of 42 pg/ml. See Table 7 of Declaration. A mean value of 42 pg/ml is clearly outside the specifically disclosed range of 100-10,000 pg/ml of IL-12 disclosed by Hadden '194. Since the composition of Hadden '194 is specifically limited to a cytokine mixture that must contain IL-12 in amounts of 100-100,000 pg/ml, the presently claimed invention which only has a mean value of IL-12 of 42 pg/ml is unanticipated by the reference.

Regarding an obviousness rejection under § 103, Applicant notes that nothing in Hadden '194 relates to the novel and

unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF where those ratios induce cancerous cells to enter a proliferative cell cycle phase thereby increasing their vulnerability to follow-on chemotherapy and radiation therapy. The revolutionary discovery of inducing cancer cells into a proliferative cell cycle with the presently claimed ratios is precisely the sort of unexpected result that imparts patentability over the broadly disclosed ranges of Hadden '194.

Based on the clear and unobvious differences from the teachings of Hadden '194, Applicant respectfully submits that the presently claimed invention is not anticipated nor rendered obvious by Hadden '194.

4. U.S. 2002/0150552 ("Lau et al. 2002/'552"), U.S. 2002/0150541 ("Lau et al. 2002/'541") and U.S. 2003/0129162 ("Lau et al. 2003/'162")

Lau et al. 2003/'162 is a published continuation-in-part application of Lau et al. 2002/'541, which is a published continuation-in-part application of Lau et al. 2002/'552.

i. Lau et al. 2002/'552 publication

Lau et al. 2002/'552 teaches human cytokine mixtures produced

by cytokine regulatory factor-overexpressing cells wherein the mixtures are prepared by culturing human cytokine-producing cells under conditions of cytokine regulatory factor overexpression, treating the cells to induce cytokine production, and isolating the mixtures of cytokines produced by the cells. See Abstract. Lau et al. 2002/'552 also teaches removing unwanted components from the cell culture medium and fractionating to segregate cytokines having selected properties such as binding affinity to particular binding agent; or which have a selected molecular weight range or range of isoelectric points. See paragraph 227.

Lau et al. 2002/'552 continues that production of a cytokine mixture can be achieved after a combination of one or more of cell line selection, modification, priming and treating. See paragraph 229. The culture medium containing the cell-produced cytokine mixture of Lau et al. 2002/'552 is then harvested and the cytokines are isolated and/or purified from the cell culture. See id. To the extent that the harvested culture medium contains suspended cells, the medium may be centrifuged at low speed, filtered, or otherwise treated to remove cells and cellular debris. The medium may be further treated by diafiltration or molecular sieve chromatography to remove low molecular weight components such as pyrogens and higher molecular weight components that are outside the molecular weight range of cytokines. See id.

To obtain a specific cytokine mixture, Lau et al. 2002/'552 teaches that the culture medium can be subjected to various protein isolation procedures which take advantage of the binding affinity of each cytokine to binding agents such as antibodies or receptors, the molecular weight or isoelectric point thereof. See paragraph 230. Exemplary procedures include antibody-affinity column chromatography, ion exchange chromatography; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; or gel filtration using, for example, Sephadex G-75. See id.

However, Lau et al. 2002/'552 fails to teach the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF that induce a cancerous cell to enter a proliferative stage which makes the cell more susceptible to follow-on radiation or chemotherapy.

ii. Lau et al. 2002/'541 publication

Lau et al. 2002/'541 adds to the disclosure of Lau et al. 2002/'552, specific examples of IFN-γ compositions that include a mixture of interferon γ and at least one of human interferon α and interferon β in a mole ratio of between 1:1 to 1:1000 interferon γ to interferon α or human interferon β. See paragraph 254. But

similar to Lau et al. 2002/'541, Lau et al. 2002/'552 does not teach the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF. Moreover, the ratios of IL-1β, IFN-γ and GM-CSF as disclosed by the reference in Table 2 at paragraph 340 are not within the claimed range.

In particular, Table 2 at paragraph 340 of Lau et al. 2002/'541 teaches IFN-γ from 1.6 ng/ml, IL-1β from <4pg/ml, IL-2 from <31 pg/ml, GM-CSF from <8 pg/ml and TNF-α from 328 pg/ml. Calculating the highest ratio of each value, the ratio of IFN-γ to IL-2 is 0.005, which is outside the claimed range of 1.5 to 10.9. IL-1β to IL-2 is 0.129, which is outside the claimed range of 0.4 to 1.5. GM-CSF to IL-2 is 0.25, which is outside the claimed range of 2.2-4.8. The novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught by Lau et al. 2002/'541.

iii. Lau et al. 2003/'162 publication

Lau et al. 2003/'162 adds to both the disclosure of Lau et al. 2002/'541 and Lau et al. 2002/'552, a preferred anti-cancer or anti-tumor composition including two or more cytokines selected from IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-12, IL-15, IFN-α, IFN-β, IFN-γ, oncostatin, TNF-α, TNF-β, GM-CSF, G-CSF, NKEF, NKSF, TRAIL

and M-CSF and more preferably selected from IL-2, IL-12, IL-15, IFN-α, IFN-β, TNF-α, natural killer cell enhancement factor (NKEF), natural killer cell stimulatory factor (NKSF), TNF-related-apoptosis-inducing-ligand (TRAIL) and GM-CSF. Notably, the composition is preferably treated to remove cytokine(s) selected from among IL-**3**, IL-5, IL-7, IL-8, IL-9, IL-10, IL-11, IL-1 and TGF-beta. See paragraph 119.

But similar to both Lau et al. 2002/'541 and Lau et al. 2002/'552, Lau et al. 2003/'162 fails to teach the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF. Again, the ratios of IL-1β, IFN-γ and GM-CSF as disclosed by the reference in Table 2 at paragraph 318 are not within the claimed range. See supra for discussion of Table 2.

Furthermore, Lau et al. 2003/'162 teaches that the cytokine mixture is treated to remove particular cytokine(s) such as IL-**3**. However, preferred embodiments of the claimed invention contain IL-3 in a ratio range of 0.38 to 0.68 to IL-2.

Based on the clear and unobvious differences over the teachings of Lau et al. 2003/'162, Lau et al. 2002/'541 and Lau et al. 2002/'552, Applicant respectfully submits that the presently claimed invention is not anticipated nor rendered obvious by any of Lau et al. 2003/'162, Lau et al. 2002/'541 or Lau et al. 2002/'552.

5. U.S. 2002/0146397 ("Hadden 2002/'397") and U.S. 2003/0206885 ("Hadden 2003/'885")

Published application Hadden 2003/'885 is a continuation application of Hadden 2002/'397, which is published application serial no. 10/015,123. For purposes of this discussion under sub-point 5, both references will be referred to collectively as the "Hadden publications".

The Hadden publications relate to a method of treating cancer and other persistent lesions including the steps of administering an effective amount of a natural cytokine mixture as an adjuvant to endogenous or exogenous administered antigen to the cancer or other persistent lesions.

The presently claimed invention is patentable over the Hadden publications because the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught. Applicant notes for the record that the Hadden publications teach that IL-3 was undetectable in all the supernatants. See paragraph 140 of Hadden 2002/'397 and paragraph 138 of 2003/'885. Trace amount for IL-3 is defined as any measured value of cytokines less than 31 pg/ml, which is the threshold detection level for ELISA produced by R&D systems.

Nothing in the Hadden publications relate to the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2

to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF where those ratios induce cancerous cells to enter a proliferative cell cycle phase thereby increasing their vulnerability to follow-on chemotherapy and radiation therapy.

Based on the clear and unobvious differences from the teachings of the Hadden publications, Applicant respectfully submits that the presently claimed invention is not anticipated nor rendered obvious.

6. U.S. 2003/0124136 ("Hadden 2003/'136") Immunotherapy For Reversing Immune Suppression

Hadden 2003/'136 relates to a method of treating cancer and other persistent lesions includes the steps of administering an effective amount of a natural cytokine mixture as an adjuvant to endogenous or exogenous administered antigen to the cancer or other persistent lesions wherein the natural cytokine mixture is preferably administered in combination with thymosin α_1. The exact same cytokine profile as that of Hadden '983 and Hadden '194 as discussed supra in sub-points 2 and 3 is taught in paragraph 68 of Hadden 2003/'136.

The presently claimed invention is patentable over Hadden 2003/'136 for the same reasons as presented supra. In particular,

the presently claimed invention recites novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF. Although Hadden 2003/'136 teaches broad ranges of the four cytokines IL-2, IL-1, TNF-α, IFN-γ and GM-CSF, the cytokine profile of Hadden 2003/'136 specifically includes IL-**12** in an amount of 100-10,000 pg/ml. See Hadden 2003/'136 at paragraph 68.

In contrast, the presently claimed composition only has trace amounts of IL-12 with a mean value of 42 pg/ml. See Table 7 of the Talor Declaration. A mean value of 42 pg/ml is clearly outside the specifically disclosed range of 100-10,000 pg/ml of IL-12 disclosed by Hadden 2003/'136. Since the composition of Hadden 2003/'136 is specifically limited to a cytokine mixture that must contain IL-12 in amounts of 100-100,000 pg/ml, the presently claimed invention which only has a mean value of IL-12 of 42 pg/ml is unanticipated by the reference.

The ranges disclosed in the cytokine profile of Hadden 2003/'136 are calculated by dividing the smallest amount of cytokine disclosed by the largest amount of IL-2. Therefore, the lower limit for the ratio disclosed by Hadden 2003/'136 for IL-1 is 10 pg/ml divided by 500 units/ml, which is 0.02. The maximum is 20, which is calculated by dividing the largest amount of IL-1 (2000 pg/ml) by the smallest value of IL-2 (100 units/ml). The

putative range of IL-1 to IL-2 is therefore 0.02 to 20 (NOTE: It is unclear as to the type of IL-1 being disclosed by Hadden 2003/''136 since only IL-1 is disclosed even though IL-1 comprises various forms such as IL-1β). The IL-2 is measured by ELISA (R&D systems), which is the same as that used by Applicant.

By making the same calculations for IL-12 it can be seen that IL-12 is disclosed by Hadden 2003/''136 to be in a ratio range of 0.2-100 and in amounts of 100-10,000 pg/ml. But as noted in the Talor Declaration, IL-12 of the claimed invention has a mean value of IL-12 of 42 pg/ml.

Applicant further notes for the record that IL-3 of Hadden 2003/''136 is present in trace amounts. Trace amounts are any measured value of cytokines less than 31 pg/ml, which is the threshold detection level for ELISA produced by R&D systems.

Regarding an obviousness rejection under § 103, Applicant notes that nothing in Hadden 2003/''136 relates to the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF where those ratios induce cancerous cells to enter a proliferative cell cycle phase thereby increasing their vulnerability to follow-on chemotherapy and radiation therapy. The revolutionary discovery of inducing cancer cells into a proliferative cell cycle with the presently claimed ratios is precisely the sort of unexpected result that

putative range of IL-1 to IL-2 is therefore 0.02 to 20 (NOTE: It is unclear as to the type of IL-1 being disclosed by Hadden 2003/'136 since only IL-1 is disclosed even though IL-1 comprises various forms such as IL-1β). The IL-2 is measured by ELISA (R&D systems), which is the same as that used by Applicant.

By making the same calculations for IL-12 it can be seen that IL-12 is disclosed by Hadden 2003/'136 to be in a ratio range of 0.2-100 and in amounts of 100-10,000 pg/ml. But as noted in the Talor Declaration, IL-12 of the claimed invention has a mean value of IL-12 of 42 pg/ml.

Applicant further notes for the record that IL-3 of Hadden 2003/'136 is present in trace amounts. Trace amounts are any measured value of cytokines less than 31 pg/ml, which is the threshold detection level for ELISA produced by R&D systems.

Regarding an obviousness rejection under § 103, Applicant notes that nothing in Hadden 2003/'136 relates to the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF where those ratios induce cancerous cells to enter a proliferative cell cycle phase thereby increasing their vulnerability to follow-on chemotherapy and radiation therapy. The revolutionary discovery of inducing cancer cells into a proliferative cell cycle with the presently claimed ratios is precisely the sort of unexpected result that

imparts patentability over the broadly disclosed ranges of Hadden 2003/'136.

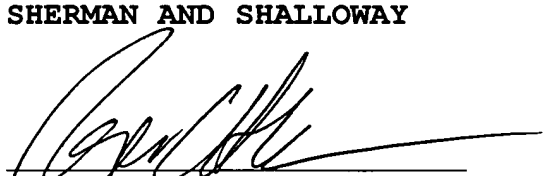
Based on the clear and unobvious differences from the teachings of Hadden 2003/'136, Applicant respectfully submits that the presently claimed invention is not anticipated nor rendered obvious by Hadden 2003/'136.

CONCLUSION

In light of the foregoing, Applicant submits the presently claimed invention is patentable. Favorable action with an early allowance of the presently pending claims is earnestly solicited. If any further communication is required to expedite the prosecution of the application, the Examiner is invited to contact the Applicant's representative.

Respectfully submitted,

SHERMAN AND SHALLOWAY



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